2020

Aldol Condensations and Nitrile Aldol Reactions Mediated by Trimethylsilyl Trifluoromethanesulfonate

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By

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Honors Thesis

In

Chemistry

University of Richmond

Richmond, VA

Spring 2020

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Acknowledgements

I would like to acknowledge and thank Dr. Wade Downey for all of his help in my successes and failures. His dedication to my learning in and out of the lab has helped to shape me into who I am today. You taught me to appreciate not only chemistry, but many other facets of life. In addition, I would like to thank fellow Downey Lab members Grant Dixon and Dani Sklar for their mentorship and friendship through the summers in the lab, as well as Pollock Lab members Joseph McEachon and Cassidy Hilton for their support. I would not be the person I am today without the influence of these people. I also want to thank all other members of the Downey lab, past and present, as everyone has affected my experience in some way. Finally, I want to thank my family, especially my late grandfather, Pop, my mom and my dad, for giving me the opportunity to attend the University of Richmond and find my way to graduation and into the future.

Abstract: In the presence of excess trimethylsilyl trifluoromethanesulfonate (TMSOTf), ketones and esters undergo aldol addition and dehydration to yield chalcones and cinnamates. This one-pot reaction proceeds through in situ enol silane formation, avoiding the need to pre-form and purify the nucleophile in the Mukaiyama aldol reaction. The stoichiometry of the TMSOTf controls whether the reaction proceeds with simple addition or addition-dehydration. When (trimethylsilyl)acetonitrile is stirred with an aldehyde and TMSOTf, nitrile aldol addition is observed.

Chapter I

Progression in organic synthesis is important for many different fields including pharmaceuticals, herbicides, pesticides, and green chemistry. Specifically, formation of carbon-carbon bond formations is of interest. Previous work in the Downey group has been focused on one-pot reactions mediated by trimethylsilyl trifluoromethanesulfonate (TMSOTf). This work has shown that TMSOTf can facilitate one-pot tandem formation of the enol silane required for the Mukaiyama aldol reaction.

The Mukaiyama aldol condensation has been very popular in organic synthesis for its ability to build molecules and attach fragments. Original conditions of the Mukaiyama aldol condensation required the use of harsh Lewis acids such as $TiCl_4$.[1] Additionally, the originally proposed reactions required pre-formation of the enol silane. Chemistry during the advent of the Downey group showed that using TMSOTf superseded the use of $TiCl_4$ in that it negated the requirement of pre-formation of the enol silane. These reactions proceeded in a one-pot tandem fashion to yield the final β-hydroxy carbonyl.

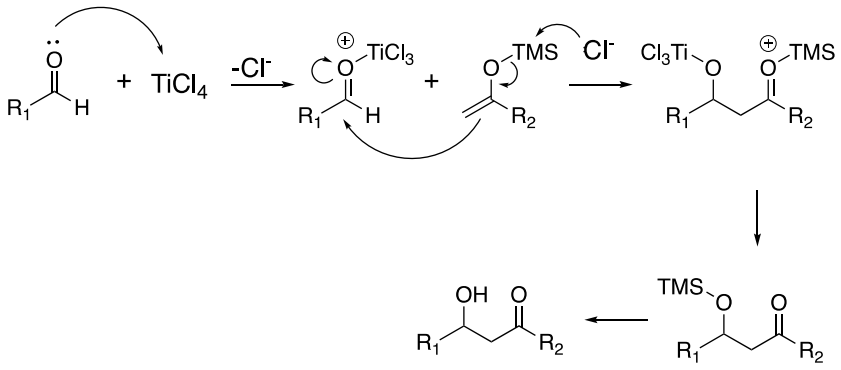
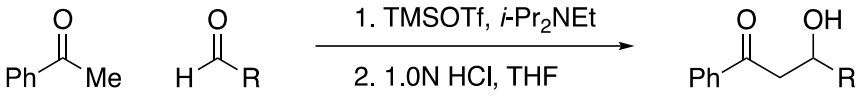


Figure 1. Traditional Mukaiyama Aldol Mechanism

[1] Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.***1974**, *96*, 7503-7509

Subsequently, our group was able to show that acetophenone and an aryl aldehyde could be combined in the presence of Hunig's base (*i*-Pr2-NEt) and TMSOTf to yield a β-hydroxy carbonyl in generally good yield, ranging from 75-96% (Eq. 1).[2] The ability of TMSOTf to act as a Lewis acid as well as a silylating agent allows the reaction to proceed in a one-pot fashion, eliminating the need to pre-form and purify the enol silane nucleophile.



Equation 1

Using this chemistry as inspiration, the work described here focuses on the synthesis of chalcones and cinnamates. In these reactions, the relative stoichiometric amount of TMSOTf determines whether the addition or elimination product forms, creating a powerful synthetic tool for future use.

[2] Downey, C.W.; Johnson, M.W. *Tetrahedron Letters*, **2007**, 48, 3559-3562

Chapter II[3]

The formation of the chalcone or cinnamate products occurs as follows: The aryl aldehyde is activated by coordination to the TMS group of the TMSOTf as shown in Figure 2. Concurrently, the amine base and TMSOTf form the enol silane in situ from the aryl ketone or acetate ester. Subsequently, the activated aldehyde can be attacked by the newly formed enol silane to produce a TMS-protected aldol product. When excess TMSOTf is present, another TMS group will be added to the already protected oxygen to form trimethylsilyl ether, an excellent leaving group. After leaving, the amine base will deprotonate the α-position, leaving the eliminated product. In the absence of excess TMSOTf, treatment with acid will convert the O-TMS group to a hydroxyl, yielding the addition product. The use of only one enolizable carbonyl reactant eliminates the possibility for mixed products.

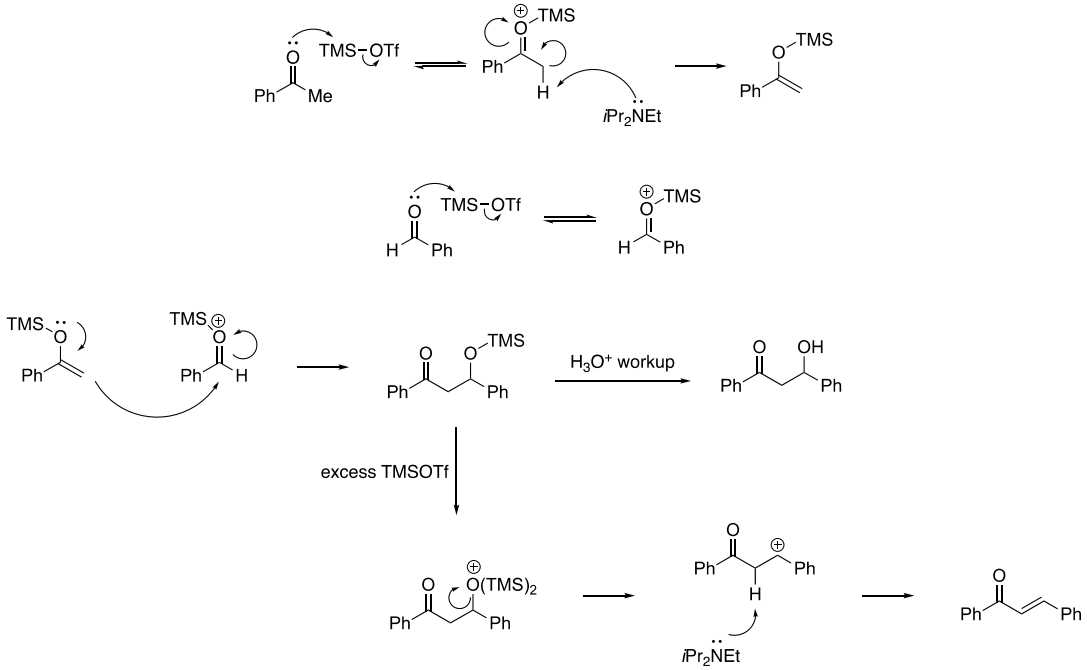
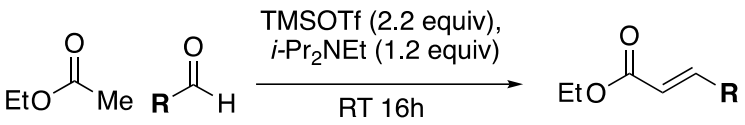


Figure 2. Mechanism for Chalcone and Cinnamate Synthesis

[3] Research done in collaboration with Hadleigh M. Glist, Anna Takashima, and Grant J. Dixon



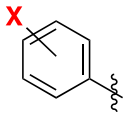
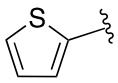
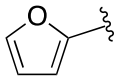
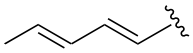
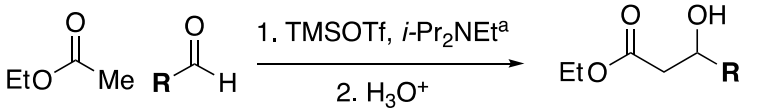
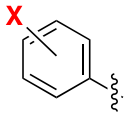
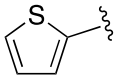
RCHO	yield (%)
 **X** = H	89
X = 4-Me	98
X = 4-OMe	70
	53
	33
	65

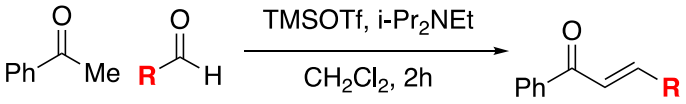
Table 1. Elimination Reactions with Ethyl Acetate



R	yield (%)
 X = 4-MeO	65
X = 4-NO2	100
X = 4-CF3	98
	53

[a] Conditions vary by substrate, but typically TMSOTf (1.2 equiv), *i*-Pr_2NEt (1.4 equiv)

Table 2. Addition Reactions with Ethyl Acetate



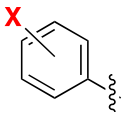
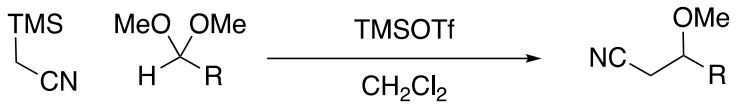
R	yield (%)
 X = H	90
X = 4-MeO	81
X = 4-F	96
X = 4-Br	91
2-naphthyl	89
2-furyl	0
2-thiophenyl	82

Table 3. Chalcone Aldehyde Scope

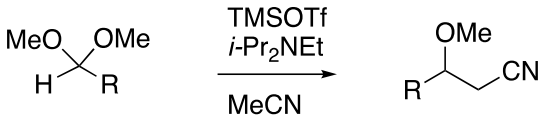
Chapter III

The Downey group has also shown that trimethylsilyl(acetonitrile) condenses with dimethyl acetals to yield *β*-methoxynitriles in the presence of TMSOTf along with Hunig's base in methylene chloride, as shown below in Equation 2.[4]



Equation 2.

Subsequently, it was shown that these same reactions could occur without using TMSACN as a starting material when the solvent is changed to acetonitrile and Hunig's base is added, as shown in Equation 3.[5]



Equation 3.

Having shown this, we wanted to expand our work to *β*-hydroxynitriles. These compounds and their derivatives provide pharmaceutically active building blocks, as well as other synthetic

[4] Downey C.W., Lee., A.Y.-K, Goodin, J.R. , Botelho, C.J., Stith, W.M., *Tetrahedron Letters*, **2017**, 58, 3496-3499
Downey C.W., Robertson G-A. L., Santa, J., Flicker, K.R., Stith, W.M, *Tetrahedron Letters*, **2020**, 61, 151537,

building blocks.[6] For example, they can be easily converted to β-amino acids, β-lactams and β-lactones, which can be further utilized to access synthetic targets.[7, 8, 9]

Methods to form β-hydroxynitriles exist in the literature but often include the use of complex metal catalysts, or enzyme catalysis.[10,11] These methods, while effective, are incredibly expensive, require the use of harsh reagents and generate considerable waste. The work described herein describes a mild route to many β-hydroxynitrile derivatives.

The first part of the proposed nitrile aldol mechanism is similar to the previously shown mechanism. The aryl aldehyde is activated and protected by TMSOTf. Subsequently TMSACN, attacks TMSOTf and then undergoes deprotonation to form a silyl ketene imine, which will act as the nucleophile. The silyl ketene imine will then attack the activated aldehyde, forming the skeleton of the final product. Through a series of TMS removals and protonations, the final product is formed.

6 Abdel-Rahman, H. M.; Hussein, M. A. Arch. Pharm. (Weinheim) 2006 339 378 387
7 Thaisrivongs, S.; Schostarez, H. J.; Pals, D. T.; Turner, S. R. J. Med. Chem.1987 30 1837 42
8 Schostarez, H. J. J. Org. Chem.1988 53 3628 31
9 Capozzi, G.; Roelens, S.; Talami, S. J. Org. Chem.1993 58 7932 6
10 Yang, Cheng, Li, *Catalysis Communications*, **2018**, 117, 38-42
11 Ankati, Zhu, Yang, Biehl, Hua, *J. Org. Chem.* **2009,** 74, 4, 1658-1662

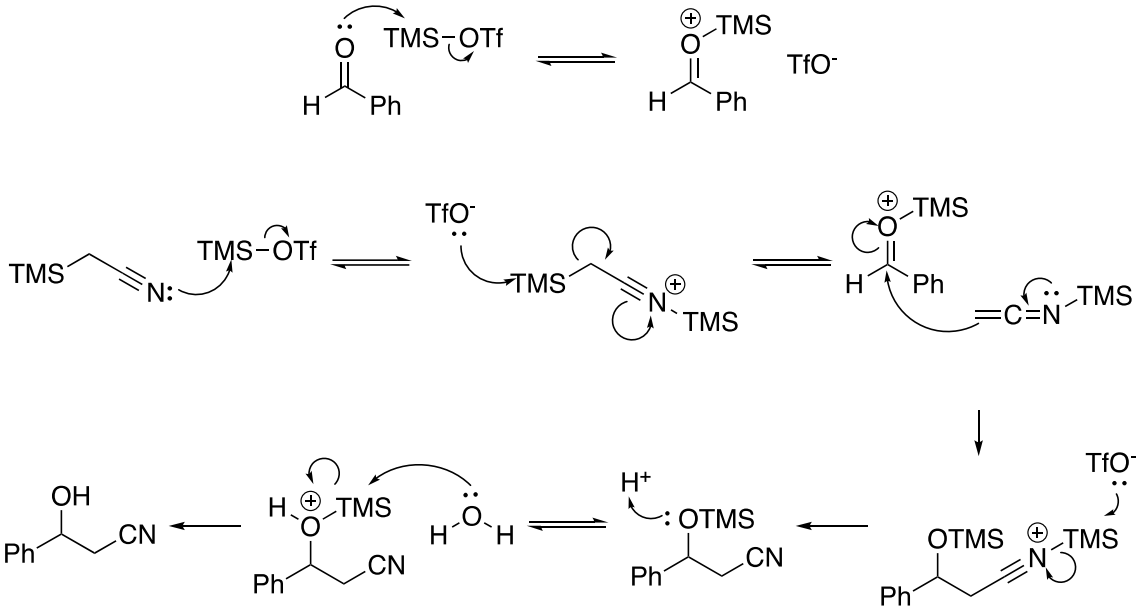
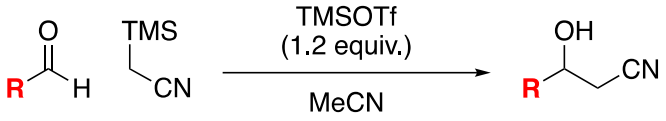


Figure 3. Proposed Mechanism for Nitrile Addition

After initial investigations were completed to optimize reaction efficiency, a scope of selected aromatic aldehydes was tested as shown in Table 4. It was found that, in general, electron withdrawing groups slow the reaction and make purification more difficult, resulting in lower yields. One important note is that the 4-nitrobenzaldehyde adduct could be produced and confirmed by ^{1}H NMR spectroscopy but was unable to be purified and isolated due to its instability across all tested chromatography conditions, including leaving the product protected during purification.



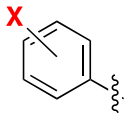
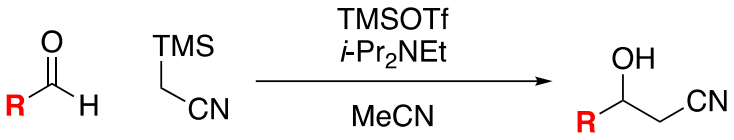
R	Yield (%)
 **X** = H	75
X = Me	86
X = 4-MeO	35
X = 4-NO_2	0
X = 4-Br	66
2-naphthyl	82
2-thiophenyl	42
cinnamaldehyde	53

Table 4. Aldehyde Scope

After getting inconsistent results with existing conditions, the presence of base was tested as an added mediator to optimize reaction rate and consistency. The first base tested was Hunig's base, which has consistently worked in many aldol reactions across the Downey group. It was discovered that while in some cases the base improved reaction outcomes, it once again lacked consistency required to extend the conditions to a large scope of aldehydes. Using benzaldehyde as a baseline, reactions that reached 100% conversion also produced high amounts of the elimination byproduct, as shown in Table. The best result obtained was using 2-thiophenecarboxaldehyde, in which the reaction was able to achieve 100% conversion in just one hour without any elimination. While this result was promising, it was not further explored due to similar work published at the same time.[12]

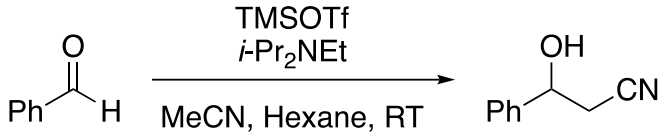
[12] Tanino, Keiji; Yoshimura, Fumihiko; Saito, Hiroki; Abe, Taiki
Synlett **2017**, 28, 1816-1820



aldehyde	Equiv. *i*-Pr_2NEt	Time	Conversion	Elimination
Ph	1.5	1 hr	70%	0%
Ph	1.5	ON	66%	0%
Ph	1.2	1hr	90%	17%
2-thienyl	1.2	1 hr	100%	0%
2-thienyl	1.5	1 hr	87%	21%

Table 5. Reactions with *i*-Pr2NEt

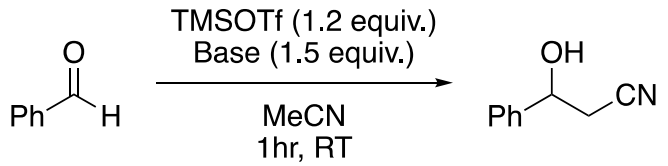
Based on the proposed mechanism, using acetonitrile as the solvent allowed us to discover that TMSOTf can convert acetonitrile to TMSACN in the presence of Hunig's base, thereby hypothetically eliminating the need to add the expensive pre-formed TMSACN. It was discovered, however, that the TMSACN generally does not form in sufficient amounts, even in the presence of Hunig's base, to result in good conversion to the nitrile aldol product. This result is in contrast to the work with dimethoxy acetal electrophiles previously shown in which the more potent oxocarbenium electrophile efficiently trapped even the small amounts of the silyl ketene imine nucleophile to produce high yields.



Equiv. TMSOTf	Equiv. *i*-Pr_2NEt	Time	Conversion
2.0	2.7	10 min	71%
2.2	2.7	10 min	78%
2.2	2.7	20 min	83%
2.2	2.7	40 min	84%
2.2	2.7	2 hr	91%
2.2	2.7	1hr	97%
2.5	3.0	10 min	87%
2.5	2.7	10 min	83%

Table 6. In-Situ TMSACN Formation

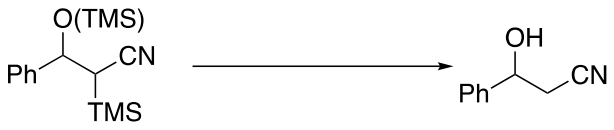
As a natural next step, the presence of other bases was explored, as shown in Table 7. All bases were subjected to the same conditions. Only Hunig's base, as previously shown, and dicyclohexylmethylamine (Cy_2NMe) showed any reactivity. Dicyclohexylmethylamine showed only 22% conversion after 1 hour and yielded only the elimination product.



Base	Conversion	Elimination
i-Pr_2NEt	72%	5%
2,6-lutidine	0%	-
N-methylmorpholine	0%	-
Cy_2NMe	22%	100%
Et_3N	0%	-

Table 7. Base Scan

One unexpected problem that arose in the course of these experiments was that of oversilylation. While silylation at the alkoxide position of the product is expected, and easily deprotected, it was seen that silylation was also occurring at the α carbon, as shown in Figure X. While typical strong acid deprotections did work to rid the α carbon of the TMS group, in many cases it also led to the formation of the undesired elimination product, also shown in Figure X (Figure X is not here that I can see). While the elimination product may be useful, there are many existing literature procedures for the preparation of this compound and is thus undesired in this case. Therefore, we experimented to find a deprotection technique that worked to deprotect the α carbon without forming the elimination product or any other unwanted byproducts. Many conditions were tested to yield the best outcome, meaning complete deprotection with limited elimination. The most consistent method was using methanol and potassium fluoride, as highlighted in Table 8 below. It is important to note that while the acetic acid/$AcONBu_4$ method also provided full deprotection with similar rates of elimination, the methanol/KF method proved to be more consistent over multiple trials and required a simpler workup.

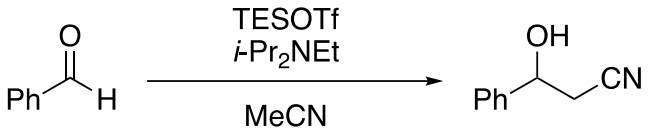


Deprotection Conditions	Time	Full Deprotection?	Elimination
MeOH/TFA	10 mins	No	-
$AcONBu_4$	1hr	Yes	50%
HCl/THF	1hr	No	-
MeOH/TFA	1hr	No	-
acetic acid/$AcONBu_4$	1hr	Yes	9%
acetic acid	1hr	No	-
MeOH, TFA, $AcONBu_4$	1hr	No	-
MeCN, H_2O, acetic acid	1hr	No	-
MeOH, acetic acid	2 hr	No	-
MeOH, KF (10 equiv.)	**1hr**	**Yes**	**10%**
MeCN, H_2O, KF (10 equiv.)	1hr	No	-
MeOH, KF (10 equiv.)	10 mins	No	-
MeOH, KF (5 equiv.)	10 mins	No	-
MeOH, KF (5 equiv.)	1hr	No	-
MeOH, KF (10 equiv.)	1hr	No	-
MeOH KF (10 equiv.)	30 mins	No	-

Table 8. Deprotection Method Testing

After finding this consistent method of deprotection, the scope of aldehydes could be further expanded, as was previously illustrated in Table 4.

After discovering the issue of oversilylation, we tested the use triethylsilyl trifluoromethanesulfonate (TESOTf) as a bulkier Lewis acid to prevent elimination products and α-silylation. The TESOTf was used in conjunction with Hunig's base in acetonitrile. It was observed that due to the bulky nature of TESOTf, the reactions generally proceeded at a slower rate, thus requiring higher stoichiometric amounts of Hunig's base and TESOTf (Table 9).



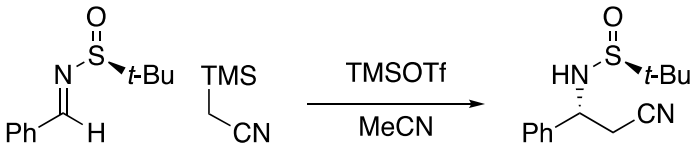
Equiv. TESTOf	Equiv. *i*-Pr_2NEt	Hexane	Time	Conversion	Elimination
2.2	2.7	Yes	1 hr	88%	0%
2.2	2.7	Yes	2 hr	85%	2%
2.2	2.7	Yes	ON	81%	1%
2.2	1.4	Yes	ON	55%	0%
1.2	1.4	No	1 hr	100%	5%
1.2	1.4	No	1 hr	89%	4%
1.2	1.4	No	2 hr	92%	0%

Table 9. Reactions with TESOTf

After experimenting with the bulkier TESOTf, we decided to test the use of triphenylsilyl chloride (TPSCl) as an even larger protecting group. It was hypothesized that if the TPS group could be used to protect the product, then it could prevent byproduct formation during the reaction, as well as during work up and purification, only requiring deprotection as a final step. However, after a series of experiments using benzaldehyde and 2-naphthaldehyde, it was discovered that our existing conditions proved ineffective for adding the TPS group to the nitrile.

Chapter IV

Having run the gamut of aldehydes and acetals, future work will focus on the use of chiral sulfinimines to enantioselectively form *α*-amino nitriles. Mukaiyama et al. have shown that the use of a Lewis base along with TMSACN can stereoselectively form this product based on the stereochemistry of the sulfinimine.[13] Initial control experiments were performed following literature procedures to test our existing conditions (Eq. 4). After discovering that our conditions were ineffective for the use of sulfinimines, we now plan to use cheap, abundant metal catalysts as a means of producing enantiopure *α*-amino nitriles.



Equation 4.

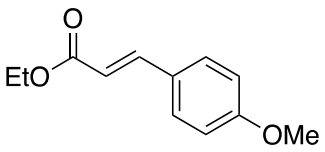
[13] Mukaiyama, T., Makoto, M., *Chemistry Letters* **2007** 36:10, 1244-1245

Chapter V

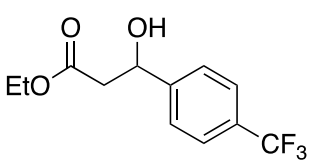
I. Aldol Condensation Experimental Section

General Information Reactions were carried under an inert atmosphere of nitrogen in oven dried glassware with magnetic stirring. Solvents were purified by passage through a column of silica. Aldehydes were purified by distillation and stored under inert atmosphere (benzaldehyde, p-fluorobenzaldehyde, cinnamaldehyde, p-trifluoromethylbenzaldehyde, p-tolualdehyde), or used as received from Millipore Sigma (4-nitrobenzaldehyde, 4-bromobenzaldhyde), or TCI (2-naphthaldehyde). TMSOTf and TESOTf from Oakwood Chemical or Millipore Sigma was stored under the inert environment of a Schlenk flask. TMSACN was used as received from Gelest Inc. Purification of reaction products was carried out using flash chromatography with silica gel (230-400 mesh). Analytical thin layer chromatography was performed on J.T. Baker Baker-Flex Gel IB-F plate. Visualization was performed under UV light followed by either CAM, 4-anisaldehyde, PMA, or $KMnO_4$ stains coupled with heating. Infrared spectra were recorded on a Nicolet Avatar 320 FT-IR Spectrometer. ^{1}H-NMR Spectra were recorded Bruker Avance 500 (500 MHz), Bruker Avance III 400 (400 MHz) or Varian 300 (300 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C-NMR spectra were recorded on a Bruker Avance 500 (500 MHz) or Bruker Avance III 400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm).

General Procedure for Reactions in EtOAc
To an oven-dried round bottom flask under N_2 atmosphere was charged EtOAc (5.0 mL). The selected aldehyde was then added (1.0 mmol), followed by Hunig's base (200 μL, 1.2 mmol) and TMSOTf (407 μL, 2.2 mmol). The mixture was stirred and then passed through a plug of silica with Et_2O. The solvent was removed in vacuo and the residue purified via flash column chromatography (0-100% EtOAc/hexanes).



2-propenoic acid-3-(4-methoxyphenyl) ethyl ester The title compound was prepared according to the general procedure using 4-anisaldehyde (120 μL, 1.0 mmol). The product was isolated as a colorless oil (144 mg, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 15.9 Hz, 1H), 7.50 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.0 Hz, 2H), 6.33 (dd, J = 16.0 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 161.3, 144.2, 129.7,127.2, 115.7, 114.3, 60.3, 55.4, 14.4; HRMS (EI, TOF) exact mass calculated for $C_{12}H_{14}O_3$ $[M+H]^+$, 207.1016. Found: 207.1010.



Benzenepropanoic acid-*β*-hydroxy-4-(trifluoromethyl) ethyl ester The title compound was prepared according to the general procedure using 4-trifluoromethylbenzaldhyde (137 μL, 1.0 mmol). The product was isolated as a white solid (213 mg, 81%): mp: 44-47 °C; IR (film)

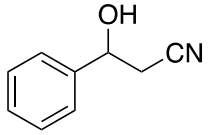
3490, 3061, 2984, 2911, 1717, 1621, 1425, 1324, 1270, 1164, 1123, 1067, 1017, 837, 737, 704; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 8.2, 2H), 7.52 (d, J = 8.2 Hz, 2H), 5.21 (ddd, J = 6.3, 3.5, 3.5 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.54 (d, J = 3.6 Hz, 1H), 2.92 – 2.62 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.1, 146.5, 129.9 (q, J = 32.4 Hz), 126.0, 125.4 (q, J = 3.8 Hz), 124.1 (q, J = 272.0 Hz), 69.7, 61.0, 43.1, 14.0; HRMS (EI, TOF) exact mass calculated for $C_{12}H_{13}F_3O_3$ $[M+Na]^+$, 285.0709. Found: 285.0708.

II. Nitrile Experimental Section

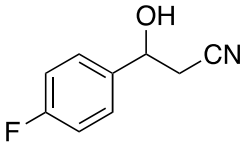
General Information: Reactions were carried under an inert atmosphere of nitrogen in oven dried glassware with magnetic stirring. Solvents were purified by passage through a column of silica. Aldehydes were purified by distillation and stored under inert atmosphere (benzaldehyde, p-fluorobenzaldehyde, cinnamaldehyde, p-trifluoromethylbenzaldehyde, p-tolualdehyde), or used as received from Millipore Sigma (4-nitrobenzaldehyde, 4-bromobenzaldhyde), or TCI (2-naphthaldehyde). TMSOTf and TESOTf from Oakwood Chemical or Millipore Sigma were stored under the inert environment of a Schlenk flask. TMSACN was used as received from Gelest Inc. Purification of reaction products was carried out using flash chromatography with silica gel (230-400 mesh). Analytical thin layer chromatography was performed on J.T. Baker Baker-Flex Gel IB-F plate. Visualization was performed under UV light followed by either CAM, anisaldehyde, PMA, of $KMnO_4$ stains coupled with heating. Infrared spectra were recorded on a Nicolet Avatar 320 FT-IR Spectrometer. ^{1}H-NMR Spectra were recorded Bruker Avance 500 (500 MHz), Bruker Avance III 400 (400 MHz) or Varian 300 (300 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C-NMR spectra were recorded on a Bruker Avance 500 (500 MHz) or Bruker Avance III 400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm).

General Procedure A for One-Pot Nitrile Aldol Reaction without Base:
To an oven-dried round bottom flask under N_2 atmosphere was charged MeCN (5.0 mL). TMSACN was then added (192 μL, 1.4 mmol), followed by the selected aldehyde (1.0 mmol) and TMSOTf (217 μL, 1.2 mmol). The mixture was stirred overnight and extracted with diethyl ether and saturated sodium bicarbonate. The solvent was removed in vacuo, and the residue was purified via flash column chromatography (0-100% EtOAc/hexanes)

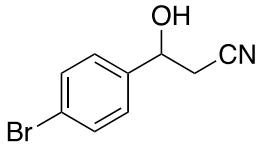
General Procedure B for One-Pot Nitrile Aldol Reaction without Base:
To an oven-dried round bottom flask under N_2 atmosphere was added the selected aldehyde (1.0 mmol), and then charged with 5.0 mL MeCN TMSACN was then added (192 μL, 1.4 mmol), followed by TMSOTf (217 μL, 1.2 mmol). The mixture was stirred overnight and extracted with diethyl ether and saturated sodium bicarbonate. The solvent was removed in vacuo, and the residue was purified via flash column chromatography (0-100% EtOAc/hexanes)



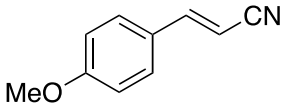
***β*-hydroxy-benzenepropanenitrile** The title compound was prepared according to the general procedure A using benzaldehyde (102 μL, 1.00 mmol). The product was isolated as a yellow oil (75% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 6.90 (m, 5H), 5.33 – 4.93 (dd, 1H), 2.80 (dd, J = 6.2, 2.0 Hz, 2H), 2.43 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.12, 128.90, 128.74, 125.61, 117.60, 69.84, 27.91.



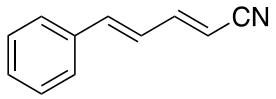
4-fluoro-*β*-hydroxy-benzenepropanenitrile The title compound was prepared according to the general procedure A using *p*-fluorobenzaldehyde (108 μL, 1.00 mmol). The product was isolated as a yellow oil (88% yield): Characterization data could not be recovered at the time of writing.



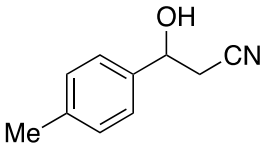
4-bromo-*β*-hydroxy-benzenepropanenitrile The title compound was prepared according to the general procedure B using 4-bromobenzaldehyde (185.02 mg, 1.00 mmol). The product was isolated as a yellow oil (66% yield): Characterization data could not be recovered at the time of writing.



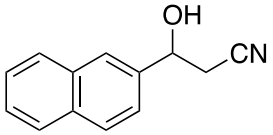
***β*-hydroxy-4-methoxy-benzenepropanenitrile** The title compound was prepared according to the general procedure A using 4-anisaldehyde (102 μL, 1.00 mmol). The product was isolated as a yellow oil (74% yield): ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 – 6.84 (m, 29H), 5.73 (d, *J* = 16.6 Hz, 1H), 5.31 (d, *J* = 12.1 Hz, 1H), 3.87 (dd, *J* = 4.9 Hz, 2H), 1.28 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.97, 129.03, 114.57, 93.50, 77.23, 76.97, 76.72, 55.42.



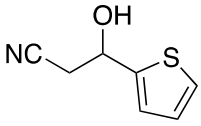
3-hydroxy-5-phenyl-4-pentenenitrile The title compound was prepared according to the general procedure A using cinnamaldehyde (125 μL, 1.00 mmol). The product was isolated as a yellow oil (53% yield): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 – 6.79 (m, 5H), 5.47 (d, *J* = 15.9 Hz, 2H), 5.28 (d, *J* = 10.7, 0.9 Hz, 2H), 1.60 (d, *J* = 0.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.76, 141.41, 127.66, 127.48, 125.48, 118.45, 116.78.



***β*-hydroxy-4-methyl-benzenepropanenitrile** The title compound was prepared according to the general procedure A using *p*-tolualdehyde (118 μL, 1.00 mmol). The product was isolated as a yellow oil (86% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.13 (m, 5H), 4.95 (dd, *J* = 7.4, 5.0 Hz, 1H), 2.38 (dd, *J* = 7.9 Hz, 2H), 1.63 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.79, 129.61, 125.43, 117.12, 70.16, 27.87.



***β*-hydroxy-2-naphthalenepropanenitrile** The title compound was prepared according to the general procedure B using 2-naphthaldehyde (156.18 mg, 1.00 mmol). The product was isolated as a yellow oil (82% yield). No column chromatography was required to purify this product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 – 6.60 (m, 5H), 5.25 (dd, *J* = 5.3 Hz, 1H), 3.23 – 2.69 (dd, 2H), 2.48 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.42, 128.16, 127.80, 124.79, 117.51, 70.08, 27.87.



***β*-hydroxy-2-thiophenepropanenitrile** The title compound was prepared according to general procedure A using 2-thiophenecarboxaldehyde (93 μL, 1.00 mmol). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.09 – 6.25 (m, 5H), 5.30 (dd, *J* = 6.5, 5.7, 0.8 Hz, 1H), 3.61 – 2.39 (dd, 2H), 1.45 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.43, 127.12, 125.80, 124.75, 117.00, 66.26, 28.23.

Chapter VI

References

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